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AD-A231714

TECHNICAL REPORT 9010

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EXPOSURE STANDARD FOR FOG OIL

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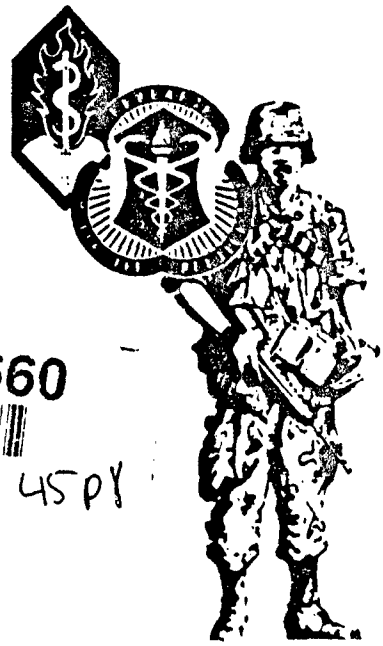
20030225047

15 November 1990

U S ARMY BIOMEDICAL RESEARCH & DEVELOPMENT LABORATORY
Fort Detrick
Frederick, MD 21702-5010



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Form Approved OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release; distribution is unlimited
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION U.S. Army Biomedical Research and Development Laboratory 6b. OFFICE SYMBOL (If applicable) SGRD-UBG-O	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, MD 21701-5010	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION U.S. Army Medical Research & Development Comman 8b. OFFICE SYMBOL (If applicable) SGRD-PLC	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, MD 21702-5012	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. / PROJECT NO. / TASK NO. / WORK UNIT ACCESSION NO.

11. TITLE (Include Security Classification)
Exposure Standard for Fog Oil

12. PERSONAL AUTHOR(S)
Winifred G. Palmer

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Technical (Revised)	FROM Dec 89 TO Nov 90	15 Nov 90	40

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	health effects, health risks, fog oil, mineral oil, exposure standard

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Effects of mineral oils in animals and humans are evaluated and serve as the basis for the development of an exposure standard for fog oil. Considered are health hazards associated with fog oil purchased before and after the Military Specification was amended in April 1986 to exclude carcinogens. While repeated exposure to conventionally-refined mineral oils may cause pulmonary disease as well as severe dermatoses and cancer of the skin and scrotum, lipoid pneumonia is the major health hazard associated with highly refined mineral oils such as fog oils purchased after April 1986. While the course of lipoid pneumonia can be asymptomatic in some individuals, in others its symptoms can range from occasional cough to severe, debilitating dyspnea and pulmonary illness, occasionally ending in death. To protect against the risk of lipoid pneumonia, an 8-hour time weighted average exposure limit of 5 mg/m^3 (for the respirable fraction) should be adopted for "new" fog oil.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT. ☐ DTIC USERS	Unclassified
22a. NAME OF RESPONSIBLE INDIVIDUAL Winifred G. Palmer	22b. TELEPHONE (Include Area Code) (301) 633-7207 22c. OFFICE SYMBOL SGRD-UBG-O

DD Form 1473, JUN 86 Previous editions are obsolete.

SECURITY CLASSIFICATION OF THIS PAGE
Unclassified

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Fog oil is a mineral oil used by the U.S. Army to create obscurant smokes. The smoke is generated by injecting fog oil into a heated manifold where it vaporizes and, on cooling in the airstream, quickly recondenses. Oil mists created in this way are composed predominantly of respirable droplets (the mass median diameter of fog oil particles was reported to be 1.16 microns;[60] exposure can occur readily via the skin and respiratory tract. Fog oil smoke is used to reduce enemy observation of troop activity and, thus, exposure is unavoidable in areas where it is used. During World War II, troops were exposed continuously to fog oil mists for up to 45 days. Among current Army personnel, the 9,232 Chemical Operations Specialists in the MOS 54B receive the greatest exposures to fog oil mists. Of these persons, the most exposed are the 6,020 soldiers between 21 and 28 years of age in grades E-1 to E-5. These soldiers may be exposed to fog oil mists for as much as 6 hours per week for an average duration of 6 years.[2]

Oil mist concentrations ranging from less than 1 mg/m^3 to 680 mg/m^3, with averages ranging from less than 1 mg/m^3 to 128 mg/m^3, were measured during a series of smoke generating exercises. Exposure levels vary with the distance from the generators, the meteorological conditions, terrain features and the mission being performed by the soldiers. Operators may be heavily exposed to smoke if the fog oil generators require frequent adjustments, if the generators are placed too close together, or if there is a sudden shift of wind speed and direction.[1,2]

PROPERTIES OF FOG OIL

Mineral oils are complex mixtures of straight- and side-chain paraffins, and naphthenic and aromatic hydrocarbons with 15 or more carbon atoms, and boiling points in the range of 300-600°C. Mineral oils vary widely in their composition, depending on their degree of refinement, boiling point range, and the source and characteristics of the crude oil from which they are produced. Some mineral oils are highly refined and are approved for use in foods or medicines. These oils (e.g., "white oil") are composed almost entirely of saturated aliphatics and contain few or no aromatic hydrocarbons. Less highly refined mineral oils are generally used for lubricating or cutting oils.

Mineral oils are classified as paraffinic or naphthenic, depending on their degree of aromaticity. Paraffinic oils are characterized by high wax content, high natural viscosity index (low rate of change of viscosity with temperature), and a relatively low aromaticity. Naphthenic oils are low in wax and relatively high in cycloparaffins (naphthenes) and aromatic hydrocarbons. Fog oil must be produced from naphthenic oils in order to meet the Military Specification for pour point and cloud point.

Its viscosity and boiling point range place fog oil in the light to middle distillate class. The viscosity of fog oil is approximately 20 mm^2/sec at 40°C (100 Saybolt Universal Seconds at 104°F). In this and other regards, it is comparable to 10W motor oil. The composition of fog oil varies from source to source[60] and with separate batches from the same source. In 1980, Katz et al. found that fog oil samples from Witco Chemical Co. and Phipps Products Corp. contained about 50 percent aromatic hydrocarbons. Acids, alcohols and esters comprised about 1 percent or less of the oil, and nitrogen derivatives

were present in the parts per million range.[60] The saturated aliphatic hydrocarbons were branched and straight chain and were primarily in the C14-C22 range. The observed aromatics included one- through four-membered ring structures. Substituted benzenes, naphthalenes, anthracenes, phenanthrenes, fluorenes, and other aromatics were identified. Nitrogen compounds included quinoline, benzoquinoline, and indole derivatives.

Katz et al. tested three different smoke generators and showed that the composition and physical properties of the smoke did not vary with the generator. In addition, the aliphatic, aromatic, and ester content of the oil smoke was similar to that of the original oil from which the smoke was generated. A slight increase in the aromatic content of the smoke was observed, indicating that the smoke-generation process caused only a slight alteration of the chemical composition of the fog oil.

Fog oil is similar in chemical and physical properties to naphthenic lubricating and petroleum-based cutting oils. These oils generally contain similar chemical species, with additives being the primary source of differences between them. The literature abounds with information on the health effects of lubricating and cutting oils, but there is little information concerning fog oil per se. Information about the health effects of fog oil can be drawn from studies of lubricating and cutting oils since their refining histories and physical and chemical properties are comparable. Although chemicals added to cutting and lubricating oil base stocks may possibly produce adverse effects, the health effects of mineral oils can be separated from those of additives with some degree of confidence. This is based on (1) the consistency between studies of the effects of additive-free oils in animals, (2) case reports of humans with exposures to highly refined mineral oils and (3) epidemiologic studies of populations with workplace exposures to mineral oil mists. However, health effects of certain cutting oils can not be related to fog oil exposures. Cutting oils can be divided into three major classes: insoluble, emulsified and synthetic oils. Insoluble cutting oils are composed of mineral oils with small quantities of extreme pressure additives. The biological response to insoluble cutting oil should be similar to that of fog oil. Emulsified cutting oils are mixtures of mineral oil and water and contain a greater complexity of additives (e.g., extreme pressure additives, antifoamers, germicides, emulsifiers, corrosion inhibitors). Care should be exercised in interpreting positive findings from health studies of workers exposed to this type of oil since they could be related to additives present in the emulsified oils. Most notably, potentially carcinogenic nitrosamines have been found in some emulsified cutting oils as a result of the use of nitrites as anti-bacterial agents.[69] Finally, synthetic oils contain no mineral oil and cannot be used for assessing the health risks of fog oil.

Like fog oil, droplets of cutting and lubricating oil mists are largely of respirable size.[58] In 1962, Hendricks[40] reported values for atmospheric concentrations of oil mists determined in work places where oils were heavily used (Table 1). Average exposure levels were below 15 mg/m^3, however concentrations as high as 56 mg/m^3 were associated with some jobs. Grupinski et al. measured oil mist concentrations in a metal machine shop as high as 110

mg/m^3 near operating machines while general room air in the machine shop averaged 87 mg/m^3.[37] In a separate machine shop study, Drasche measured oil mist concentrations between 50 and 150 mg/m^3.[27]

TABLE 1

EXPOSURE TO OIL MIST IN SELECTED INDUSTRIES PRIOR TO 1962

Industry	Oil Concentration (mg/m^3)	Number of Observations
Brass & Aluminum Production	1.4-20.7	5
Copper mining	5.4-22.0	7
Automobile manufacture	1.0-56.5	37
Manufacture of steel products	0.8-50	33
Newspaper (pressroom)	2.0-16.6	8
Screw manufacture	1.0-14.2	6

Data taken from Hendricks[40]

It has been known for decades that workers exposed to mineral oils in the jute, cotton spinning, and metal machining industries have an elevated incidence of skin cancer of the hands, arms and scrotum. The carcinogenicity of mineral oils, first observed in humans and later confirmed in experimental animals, is largely attributed to polycyclic aromatic hydrocarbons (PAH) and related heterocyclic compounds.[9,39,52,59] In 1985, the International Agency for Research on Cancer (IARC) concluded that untreated naphthenic oils are carcinogenic.[52] In 1986, the Military Specification for fog oil was modified to reflect these concerns.[26] The modified specification excluded all "carcinogenic or potentially carcinogenic constituents". (For the purpose of brevity, fog oils obtained before the specifications were changed in 1986 are referred to as "old" fog oil and those purchased later are referred to as "new" fog oil.)

Oil producers use either severe hydrotreatment or severe solvent refining to meet the 1986 specifications. Solvent refining selectively removes PAH and some sulfur and nitrogen compounds by extraction of oils with organic solvents such as furfural, phenol and N-methylpyrrolidone. Hydrotreatment involves low pressure, catalytic reduction of carbon-carbon double bonds. With the latter process, aromatics can be converted to saturated cycloparaffins (naphthenes) and heterocyclic aromatics can undergo ring opening, with chemical removal of bound sulfur, nitrogen and oxygen. Thus, solvent extraction physically removes some of the undesirable compounds from the oil, while hydrotreatment converts them to less toxic, saturated compounds. The heat used in

hydrotreatment may also create new compounds by 'cracking', with reduction in size of some of the larger molecules.

The severity of hydrotreatment dictates the degree of saturation of carbon-carbon double bonds. Mild hydrotreatment at low hydrogen pressures and/or temperatures is not sufficient to remove carcinogens[39] and may actually increase the mutagenicity of an oil.[102] However, if appropriately severe, hydrotreatment can substantially reduce or eliminate the carcinogenic potential of lubricating oils.

EFFECTS IN HUMANS

The best documented health effects of the lubricating oils are pulmonary lipoid granulomas and pneumonia, skin irritation, dermatoses, and skin cancer. Some studies have associated cancer of other organs with exposure to lubricating oils. These cancers are less well documented and, in some cases, may have been associated with secondary exposures to other chemicals (e.g., newspaper pressmen).

Skin Lesions

Contact with lubricating oils can irritate the skin. Short exposures may cause only mild erythema, while prolonged and repeated contact with conventionally-refined lubricating oils or oil mists can cause inflammation, dermatitis, folliculitis, acne, eczema and contact sensitivity.[20,64] (The term 'conventionally-refined' is used here to describe lubricating oils that have not been severely hydrotreated or solvent refined and are likely to contain PAHs and related heterocyclic aromatic compounds.) Malignant and premalignant skin changes (e.g., hyperkeratosis, benign papillomas) may be caused by exposure to poorly refined lubricating oils. These conditions are generally attributed to the PAH content of the oils. This is supported by mouse skin painting studies (see below) which show that highly refined naphthenic oils are not tumorigenic. Thus, serious chronic skin conditions can result from exposures to "old" fog oil but are not likely to be a problem with "new" fog oil.

Oil acne is common among workers exposed to poorly refined cutting and lubricating oils. The back of the hands and thighs are the areas most often affected. In 1970, Hodgson reported that 15 to 18 percent of all cases of industrial dermatitis are due to cutting oils. This figure would be still higher if the number of cases of industrial dermatitis resulting from exposure to lubricants was included.[45] In 1950, Cruickshank found oil folliculitis in 80 percent, and warts in 33 percent of 138 machine shop workers from 3 separate factories. The number of men with hyperkeratoses or warts increased with years of exposure; warts were found on 4 percent of the workers with 2 to 5 years exposure and on more than 50 percent with 16 to 20 years exposure.[20]

Cancer of the Skin and Scrotum

The evidence for an association between skin cancer of the hand, arm and scrotum and exposures to conventionally-refined mineral oils is overwhelming. Many case reports and epidemiologic studies of this association have been published and reviewed.[1,52,64] IARC reviewed epidemiologic studies of metal workers, printing pressmen, oil refinery workers, jute workers and cotton mule spinners.[52] They concluded that there is sufficient evidence "that mineral oils (containing various additives and impurities) that have been used in occupations such as mulespinning, metal machining and jute processing are carcinogenic to humans". While many oils used in these practices are similar in composition to fog oil, they may also contain additives not present in fog oil. However, animal skin painting studies (see below) indicate that the carcinogenic potential of conventionally-refined lubricating oils is due to the components of the oils themselves, in particular the PAH fraction, and not necessarily to additives.

The use of automatic machines which required cutting oils increased rapidly after World War I. Sprays emanating from the machines and from direct contact with oil-coated surfaces caused gross contamination with mineral oil, especially in the lower abdominal area. It has been recognized since the early 1950s that metal workers repeatedly exposed to lubricating and cooling fluids during cutting and grinding of metals may develop tumors of the skin of the scrotum, arms and hands.[20,21] In 1955, it was reported that six cases of squamous cell carcinoma of the hands and forearms and one of the scrotum occurred over a 12 year period (1944 to 1955) among seven cutting-oil exposed machine operators from a single engineering plant in Canada.[66] Oils used by these workers were subsequently shown to be carcinogenic in mouse skin painting studies.[34,35]

In 1950, records of the British Ministry of Social Security, Productivity and Employment showed that as many as 60 percent of workers exposed to liquid cutting lubricants for over 15 years developed chronic inflammatory and cancerous changes on the hands, forearms and scrotum.[46] At least 1441 cases of skin cancer were attributable to industrial exposures to mineral oil in the United Kingdom between 1920 and 1943.[6] Waldron et al. examined the incidence of scrotal cancer in the West Midlands of England, a region with a high concentration of engineering and metalworking companies. Between 1936 and 1976, there were 344 cases of scrotal cancer. Of the 316 cases for which occupations could be identified, 213 had been exposed to mineral oil; 89 of these men had been tool setters and tool fitters.[106]

Excess scrotal cancers were identified in a case-control study conducted in Connecticut of workers exposed to cutting and/or mineral oils.[85] A high incidence of skin cancer was also observed in metal workers in the Cluses area of France. Thony and Thony[99,100] identified benzo(a)pyrene (BaP) and other PAH in lubricating oils used in this region.

High rates of skin and scrotal cancer were also noted in jute and cotton textile workers with high levels of exposure to mineral oils. Jute workers were exposed to mineral oil/water emulsions used to soften and lubricate natural fibers before spinning. Premalignant skin changes (keratoses) were

seen in 7.2 percent of 3023 workers in jute establishments in Scotland.[61] It has been known since early in this century that cotton textile workers with long-term exposure to mineral oils used to lubricate a machine called the spinning mule had a high incidence of skin and scrotal cancer ("mule spinners disease").[94] The incidence was particularly high in Great Britain where 1330 cases were reported between 1920 and 1945[41] Recently, Castiglione et al. described a 66-year-old cotton textile worker who, after frequent abdominal contact with mineral oils, developed multiple squamous cell carcinomas of the scrotum.[15]

Scrotal cancer is uncommon in men with no history of exposure to mineral oil. Hodgson[46] showed that most workers in the metal machining, cotton and jute industries with scrotal cancer had at least six years of exposure to mineral oils and were between 40 to 50 years of age whereas scrotal cancer usually does not appear in non-exposed men until after 70 years of age.

In recent years, the incidence of skin and scrotal cancer in textile workers and machinists has declined substantially,[11,29] although cases of scrotal cancer in workers with mineral oil exposures continue to be reported.[15] The decline in the rate of skin cancer is attributed to the introduction of oil refining processes which reduce the PAH content of the oils.[11,29]

Cancer of Other Organs

The evidence for an association between mineral oil and cancer of organs other than the skin and scrotum is far less conclusive. Some investigators have observed excesses of lung cancer in oil exposed workers[16,101] while others have not.[25,54,91] Siemiatycki et al.[91] performed a population-based, case-referent sudy of the relationship between several types of cancer and exposure to petroleum derivatives. The study population included 3726 cancer patients diagnosed in 19 hospitals in Montreal, Canada. Only a weak association between exposure to lubricating oils and squamous-cell carcinoma of the lung was found. The association between lung cancer and exposure to cutting oils was negative.

A proportional mortality study conducted in machine shop areas of three Kodak plants in New York State[28] showed no excess deaths from cancers at all sites combined or from respiratory tract cancer, Hodgkins's disease or leukemia. Exposures were to oil mist in concentrations ranging from 0.7 to 110 mg/m^3 (median concentration, 1.5 mg/m^3; mean concentration, 3.7 mg/m^3).

Some data indicate that men with mineral oil-related cancers of the scrotum may also develop primary tumors at sites other than the skin. Holmes et al.[49] and Waterhouse[107] examined the records of 187 primary cases of epithelioma of the scrotum in the Birmingham Regional Cancer Registry for 1950 to 1967 and found a significant excess of primary cancers of the respiratory and upper digestive tracts. The oil exposed workers with scrotal cancer had significant excesses of subsequent primary tumors of the skin (5 observed vs 0.81 expected; $p = 0.001$), respiratory (3 observed vs 2.52 expected;

p = 0.C04) and digestive tracts (7 observed vs 2.55 expected; p = 0.015). Later studies indicated that an even greater number of men (about 15 percent) with scrotal cancer had second primary tumors at sites other than the skin.[105]

Malignant melanoma and gastrointestinal tract, sinonasal, bladder and lung cancer were noted in other studies in which there was exposure to cutting or lubricating oils. However, in each of these studies substantial exposures to reactive materials other than mineral oils was likely. An excess of gastrointestinal tract cancer, but not respiratory tract cancer, was found in a cohort study of 2485 men from a single American plant who had been exposed to cutting oil mists for at least five years. Men in the study cohort had experienced mixed exposures to synthetic, emulsified and insoluble cutting oils.[24,25] An association between gastric cancer and machine oil exposure was also found in a cancer mortality study of a large number of workers in various Japanese industries.[73] Roush[84] found an elevated risk for sinonasal cancer in a case-control study of persons exposed to cutting oils (occupations included toolsetter, set-up man and toolmaker).

Few of the epidemiology studies of occupations with high oil exposures reported oil mist concentrations to which workers were exposed. For most studies, little information was available concerning the chemical makeup of the oil exposures.

Ronneberg et al.[82,83] reported an increase in respiratory disease and lung cancer in workers in a Norwegian cable manufacturing company who had continuous exposures to naphthenic mineral oils. However, asbestos was used in some processes at this plant and may have influenced the lung pathology. Several studies cited by IARC[52] suggested that jobs classified as machinist, engineering fitters or engineers are associated with an elevated risk of bladder cancer. However, they noted that these observations may have been related to additives (in particular aromatic amines).

In their investigation of etiological factors involved in the development of cutaneous malignant melanomas, Bell et al.[8] found that the risk for malignant melanoma was significantly elevated in workers exposed to cutting oils but not in those exposed to mineral oils. These investigators concluded that the risk for melanoma was probably related to additives (e.g., nitrosamines) in cutting oils and not to components of the base mineral oil.

Respiratory Effects

Whereas skin lesions and cancer of the skin and scrotum have been attributed largely to the PAH content of conventionally-refined lubricating oils, pulmonary effects such as granulomas and pneumonias can occur with exposure to highly refined mineral oils which lack PAH. According to IARC, over 400 cases of lipoid pneumonia were reported in the literature before 1978 and were related to ingestion of mineral oil, inhalation of oil-based nose drops or intralaryngeal injection of medicinal oil.[52]

Two forms of lipoid pneumonia can result from mineral oil exposure. The first, lipoid granuloma or paraffinoma, is a circumscribed lesion within a single lobe of the lung which is easily mistaken for a tumor. If destruction of lung tissue is extensive, this type of lesion can lead to a great loss of pulmonary function.[53]

The second type of lipoid pneumonia is diffuse pneumonitis in which oil droplets are widely disseminated throughout one or more lobes of the lung. It may be accompanied by bacterial infections. The course of lipoid pneumonia can be asymptomatic in some, while in others its symptoms can range from occasional cough to severe, debilitating dyspnea and pulmonary illness, occasionally ending in death. It sometimes produces no changes in x-ray profiles and can be diagnosed only by lung biopsy or other invasive procedures. Lipoid pneumonia frequently causes fibrosis which, in advanced cases, can result in loss of pulmonary function. Depending on the degree of inflammation that occurs, damage to the lung can be slight or can fulminate to necrosis and hemorrhage.[18,53,64,78,98]

Lipoid pneumonia is uncommon in the workplace, even in areas where oil mist concentrations are over 50 mg/m^3.[64] In 1962, Hendricks reported the findings of the American Petroleum Institute survey of the health status of workers exposed to mineral oil mists. The survey revealed no instances in which lung abnormalities were associated with oil exposure. Complaints from surveyed workers indicated that discomfort occurs at oil mist levels greater than 5 mg/m^3. According to Hendricks, these findings were corroborated by a survey performed by the Detroit Bureau of Industrial Hygiene which showed that there are few complaints when oil concentrations are less than 5 mg/m^3. No indications of lung "difficulties" were noted among exposed workers in the Detroit study.[40]

Hendricks concluded that a sizable population of workers, in a variety of occupations, is exposed to oil mist. In most cases, average exposure levels are below 15 mg/m^3 but higher exposure levels are associated with some jobs. In view of the size of the exposed population, Hendricks found a striking lack of reported cases of respiratory illness associated with the inhalation of oil mist. Although he did not believe that higher exposures are likely to lead to pulmonary impairment, he concluded that a maximum allowable exposure of 5 mg/m^3 would avoid "nuisance and subjective complaints".

Jones[58] examined 19 workers from a steel rolling mill who had been exposed 2 hr/day to oil mist concentrations as high as 9 mg/m^3 for 9 to 18 years. The oil used at the time of the study was a naphthenic spindle oil containing petroleum sulfonates, rosin soap and cresylic acid. There was no evidence of lipoid pneumonia, lipoid granuloma, bronchitis, diseases of the nose and throat, or skin or gastric disorders in any of the workers. The only possibly significant finding was an increase in linear striations in the lungs of 12 men. The importance of this X-ray pattern was unknown.

NIOSH examined 25 workers exposed to mineral-water emulsions in an automobile drum and disk brake manufacturing plant. Oil mist concentrations averaged 2 mg/m^3. Although minor respiratory tract infections tended to be unusually persistent among the workers, no association could be made between respiratory tract symptoms and occupational exposure to oil mist.[44]

Drasche et al.[27] investigated the frequency of respiratory complaints (cough, expectoration, dyspnea) in 443 machine metal workers chronically exposed to drilling and cutting oils in concentrations of 40 to 150 mg/m^3. No signs of respiratory tract irritation were observed.

No changes in pulmonary function were noted in three studies of oil exposed workers. Jarvholm and Thiringer[55] found no differences in respiratory symptoms, chest x-ray patterns and the spirometric measures forced vital capacity (FVC) and one second forced expiratory volume ($FEV_{1.0}$) between 168 machine shop workers and 165 office worker controls. These investigators later[56] observed a tendency for excess respiratory symptoms (cough and phlegm) in non-smoking machine shop workers. Median oil mist exposures ranged from 1.1 to 4.5 mg/m^3 in different departments. The prevalence of respiratory symptoms was greater in workers from areas with higher oil exposures. Since the oils contained more additives in areas where exposures were greatest, it is difficult to separate the effects of additives from those of mineral oils in this study.

Two studies reported in the Russian literature indicated that changes in pulmonary function may be associated with chronic exposure to mineral oils. Textile workers who were exposed to spindle oil mists for ten or more years had a diminution in vital capacity, forced vital capacity and minute volumes.[5,14]

Ely et al.[28] conducted a "prevalence study" of more than 1700 machine shop workers who were exposed to oil mist concentrations ranging from 0.7 to 110 mg/m^3 (median concentration, 1.0 mg/m^3; mean concentration, 5.2 mg/m^3). No abnormalities in the incidence of cough, bronchitis, wheeze and dyspnea or in two measures of pulmonary function, $FEV_{1.0}$ or FVC, were noted.

In 1979, Oxhoj et al. examined 385 cutting-oil exposed machine shop workers in 27 plants in Copenhagen. Exposures ranged from 0.1 to 2 mg/m^3 (median 0.35 mg/m^3). A positive association was found between the concentration of oil mist and chronic cough and phlegm in smokers while no respiratory effects were seen in non-smokers. There was no association between the type of oil (mineral oil, emulsion, semisynthetic or synthetic cutting oils) to which workers were exposed and the prevalence of respiratory disease.[75]

Scattered case reports have been published which attribute occupational oil exposures to respiratory disorders in individual workers.[22,78] Proudfit[78] reported the case of a 40-year old man with chronic lipoid pneumonia that apparently resulted from occupational exposures. The subject had worked as a repair man for 17 years during which time he was routinely exposed to heavy mineral oil mists in semi-confined spaces. He had a chronic cough, frequent colds and substantial loss of pulmonary function.

Cullen et al.[22] examined nine oil-exposed workers with respiratory tract symptoms from a steel rolling plant. Five of them experienced dyspnea on exertion, recurrent acute and chronic cough, upper airway irritation, and skin rash. The most severely affected worker had lipoid pneumonia. These workers were exposed to three types of oils: commercial grade kerosene, a water-soluble coolant of unknown composition, and a blend of refined petroleum heavy paraffinics containing 15 to 20 percent aromatics with a boiling point range of 600 to 900°F. Average oil mist levels were 0.7 mg/m^3. In addition, they were also exposed to toluene (less than 100 ppm). Cullen concluded that relatively low levels of mineral oil mist can cause respiratory disease. However, the substantial exposures to toluene and kerosene received by these workers makes it impossible to relate their symptoms to mineral oil. Thus, evidence concerning lubricating or fog oil effects on the lungs cannot be inferred from this study.

In conclusion, studies of nonoccupational human exposures clearly show that inhalation or aspiration of mineral oils can cause severe lipoid pneumonia. While there are scattered reports linking respiratory disease with occupational exposures to mineral oil, the bulk of the studies of workers chronically exposed to mineral oils indicate that oil mist levels commonly found in industry are unlikely to cause serious respiratory tract changes.

ANIMAL STUDIES

Acute Effects

Tests in rats and rabbits showed that single dermal or oral applications of "old" fog oil, and paraffinic and naphthenic lubricating oils are low in acute toxicity (Table 2).[7,67] Gerarde[32] observed no mortalities among Wistar rats after aspiration of 0.2 ml mineral oil or multigrade motor oil; one of five rats died after aspirating a second dose of multigrade motor oil. The investigators concluded that aspiration of lubricating oils does not cause the severe pulmonary edema or hemorrhage characteristic of kerosene and similar low-viscosity hydrocarbon mixtures.

Short-term Skin Exposures

Single topical applications of mineral oils cause slight to moderate irritation (Table 2).[7,67] Repeated application of lubricating oils is more damaging to skin than single applications.[96] Hoekstra and Phillips[47] showed that conventionally-refined light mineral oils caused marked epidermal hypertrophy, hyperplasia, hyperkeratosis and depilation when applied every other day for one week to the skin of male albino guinea pigs. Related experiments with purified compounds showed that the ability to cause skin damage was not confined to aromatic hydrocarbons. Of the non-aromatic compounds, application of hydrocarbons with carbon numbers in the range C14 to C19 caused the greatest skin injury. Aliphatic hydrocarbons with greater than 21 to 23 carbon atoms were not dermatotoxic.

Neither paraffinic nor naphthenic lubricating oils induced dermal sensitization in guinea pigs[7].

TABLE 2

ACUTE TOXICITY VALUES

Test Article	Results	Species	Reference
PRIMARY DERMAL IRRITATION			
"Old fog oil"	moderate	NZW rabbit	Mayhew[67]
Paraffinic lube oil	minimal	NZW rabbit	Beck[7]
Naphthenic lube oil	slight	NZW rabbit	Beck[7]
EYE IRRITATION			
"Old fog oil"	negative	NZW rabbit	Mayhew[67]
Paraffinic lube oil	negative	NZW rabbit	Beck[7]
Naphthenic lube oil	negative	NZW rabbit	Beck[7]
DERMAL LD50			
"Old fog oil"	> 2 g/kg	NZW rabbit	Mayhew[67]
Paraffinic lube oil	> 2 g/kg	NZW rabbit	Beck[7]
Naphthenic lube oil	> 2 g/kg	NZW rabbit	Beck[7]
ORAL LD50			
"Old fog oil"	> 5 g/kg	Fischer rat	Mayhew[67]
Paraffinic lube oil	> 5 g/kg	SD rat	Beck[7]
Naphthenic lube oil	> 5 g/kg	SD rat	Beck[7]

NZW = New Zealand White
SD = Sprague Dawley

Long-term Effects

Oral

Chronic ingestion of highly refined mineral oils is not known to cause cancer in animals. Tumors were not induced in rats given 2 percent liquid paraffin (comparable to medicinal grade mineral oil) in the diet for 500 days.[87] In a separate study, no oil-related tumors were observed in rats fed 5 percent diets of three grades of petrolatum (comparable to medicinal grade mineral oils) for 2 years.[74]

Injection

Highly refined mineral oils have been tested for tumorigenicity by intraperitoneal, intramuscular and subcutaneous injection (See Ref. 52 for review). No tumors developed in Swiss-Webster mice following single subcutaneous injections of three types of medicinal grade mineral oils.[74] Intraperitoneal injection of food grade mineral oils caused plasma-cell neoplasms and reticulum cell sarcomas in Balb/c[77] and DBA/2[79] mice, respectively.

Inhalation

Shoshkes examines the pulmonary response of mice to very high atmospheric concentrations of animal, vegetable, mineral (USP grade liquid petrolatum) and SAE No. 10 Motor oil. The "edible" oils (corn, peanut and cod liver oil) cleared much more rapidly from the lungs than did the mineral and motor oils, which was attributed to differences in susceptibility to hydrolysis by lipases. Two-hour exposures to the oils caused only the appearance of scattered macrophages, with no acute inflammatory changes. However, 4-week exposures to high concentrations of mists of mineral, but not edible oils were associated with localized foreign body reactions of moderate severity and patches of lipoid pneumonia.[90]

Costa and Amdur tested the effects of single exposures to submicron petroleum oil mists on respiratory function (tidal volume or minute volume) in guinea pigs. Animals were exposed for one hour to concentrations ranging from 10 to about 250 mg/m^3 of each of the following: medicinal grade mineral oil, laboratory grade paraffin oil, light lubricating oil Grade S-75 and SAE 10W-30 motor oil. None of the oils at concentrations of 10 or 40 mg/m^3 produced alterations in pulmonary function. A significant response was observed only with light lubricating oil which caused a decrease in pulmonary compliance at concentrations greater than 200 mg/m^3.[19]

Lushbaugh[65] exposed monkeys and CF1 mice to mists of automobile lubricating oil SAE No.10 (132 mg/m^3, 30 min/hr, 24 hr/day for up to 100 days) and rats, rabbits, monkeys and strain A mice to diesel engine lubricating oil SGF No. 1 (63 mg/m^3 for up to one year). The very small amounts of oil retained in the lungs of exposed mice, rats and rabbits produced no lipoid pneumonia and little evidence of inflammation in any of the animals. Macrophages with disperse small oil droplets were seen throughout the lungs. The number of alveolar macrophages increased from week 1 through week 5 and then remained fairly constant through the remainder of the study.

The oils caused hair loss and severe pulmonary effects in monkeys, which accumulated a higher concentration of oil in their lungs than did mice exposed to comparable quantities of oil for the same periods. SGF No. 1 oil was substantially more toxic than SAE No. 10 oil. Two of six monkeys died within 100 days of exposure to SAE No. 10 oil while exposure to the SGF No. 1 oil killed 6 of the 7 animals tested. Autopsy revealed infectious pneumonitis, pulmonary lipophages and severe hyperplastic gastritis (presumably from swallowing inhaled oil) in animals exposed to either type of oil.

The numbers of alveolar macrophages increased with time. Diffuse pneumonitis was observed after 44 days exposure to SGF No. 1 oil and a small area of acute pneumonia with edema was seen after 58 days of exposure to SAE No. 10 oil. Diffuse acute bronchopneumonia with edema and hemorrhage, lobular pneumonia, diffuse pneumonitis and fibroplasia were found in monkeys with longer exposures to either oil. Fibroplastic nodules containing macrophages rich in oil were seen in two monkeys after 64 and 265 exposure-free days following the 100-day exposure period. Although the incidence of infectious pneumonia was greatly increased, the cause of death in most of the treated monkeys was determined to be severe hyperplastic gastritis.

Wagner et al.[103] examined the effects of long-term exposure of 5 species to mists containing 5 or 100 mg/m^3 mineral oil (mean particle diameter = 1.3 microns). The "light" mineral oil (Saybolt viscosity 85 to 95) used in this study contained 5 percent paraffins and 95 percent one- to six-ringed saturated naphthenes. This naphthenic-based fully saturated oil was comparable to "new" fog oil.

Of the species tested (rat, rabbit, dog, hamster and mouse), rats and dogs were most affected by the mineral oil mists (Table 3). Exposures to 100 mg/m^3 for one year caused pulmonary lipoid granulomas in the dog and pneumonitis in the rat. Findings of "a few fibrotic strands" in the granulomata of the lung parenchyma and hylar lymph nodes suggested that continued exposure may have produced a progressive fibrosis with a consequent impairment of pulmonary function. No pathologic response to 5 mg/m^3 mineral oil was observed in any species.

Serum alkaline phosphatase (AP) levels correlated well with histopathologic findings in the dog, rat, and rabbit. In the hamster, AP was elevated in lung tissue even though there was essentially no histopathologic response to mineral oil in the lung (serum AP was not measured). Wagner concluded that changes in AP can be used as an indicator of the early response to injury from pulmonary irritants.

Two separate studies examined the effects of mineral oil on the lung tumor incidence in mouse strains that are highly susceptible to lung tumors. Exposure to diesel engine lubricating oil SGF No. 1 at 63 mg/m^3 for up to one year did not alter the incidence of lung tumors in Strain A mice.[65] Wagner et al.[103] exposed CAF_1/Jax mice to 5 and 100 mg/m^3 mineral oil for 13 months. CAF_1/Jax mice are highly susceptible to lung tumor development and have a relatively high rate of spontaneous lung tumors. Neither dose altered the incidence of lung tumors.

TABLE 3

EFFECTS OF LONG-TERM EXPOSURE OF 5 SPECIES TO 5 AND 100 mg/m^3 MINERAL OIL[a]

Test Exposure	Percent increase in alkaline phosphate (AP) BAP 5	BAP 100	MgAP 5	MgAP 100	Pathology
Rabbit					
0-18 mo	0	0	0	0	No pathologic response; Occasional foamy macrophage
Dog					
12 mo	0	90%[b]	0	70%[b]	6 mo: occasional macrophage at 5 and 100 mg/m^3.
18 mo	0	112%[b]	0	62%	12 mo: 100 mg/m^3: granulomas in alveolar spaces, hylar lymph nodes & near smaller bronchi.
Rat					
6 mo	0	84%	0	58%	5 mg/m^3: No pathologic response
12 mo	0	64%[b]	0	41%[b]	
	0	NG[c]	0	NG[c]	100 mg/m^3: duration-related accum. of macrophages; varying degrees of interstitial pneumonitis.
Hamster					
9 mo	0	216%[b,c]	0	207%[b,c]	15 mo: No pathologic response Occasional foamy macrophage
Mouse	-	-	-	-	12 mo: No major pathologic response; Slight accumulation of macrophages

[a] Mineral oil used comparable to "new" fog oil.
[b] statistically significant
[c] lung tissue enzyme (all other data is for serum enzymes)
Only serum AP alone tested in dog and lung AP tested in hamster.
- = not tested
NG = data not given
MgAP = magnesium activated alkaline phosphatase
BAP = basic alkaline phosphatase
Data taken from Wagner[103]

Selgrade et al[89] and Grose et al[36] examined the effects of single and repeated exposures of rats to "old" fog oil mists composed of droplets approximately 1 micron in diameter. A concentration of 1000 mg/m^3 was lethal to 20 percent of the animals exposed for 6 hours but not to animals exposed for 3.5 hours. With 3.5 hour exposures, the LC50 was 5200 mg/m^3 and the dose response was very steep; less than 15 percent of the animals died at 4000 mg/m^3 and over 80 percent died at 6000 mg/m^3.

In a 4-week subchronic study, Grose et al[36] exposed rats to doses of 500 and 1500 mg/m^3 for either 70 minutes or 3.5 hours/day for 2 or 4 days/week. The results of this study are summarized in Table 4. A dose-related accumulation of alveolar macrophages occurred with all exposures; the effect at 500 mg/m^3 was minimal to slight for all time periods. Wet and dry lung weights were elevated in high dose animals exposed for either 2 or 4 days. Total lung protein, total cell count and polymorphonuclear leukocytes (PMN) were elevated in bronchoalveolar lavage fluid (BAL) from high-dose animals. These changes are consistent with mild inflammatory pulmonary edema. Pneumonitis, as characterized by "multifocal hypercellularity of the alveolar wall, associated with an interstitial infiltration of subacute inflammatory cells" was seen in 4 of 6 males exposed at 1500 mg/m^3 for 3.5 hours/day, 4 days/week and in no other rats.

TABLE 4

EFFECTS OF 4-WEEK EXPOSURE OF RATS TO FOG OIL MISTS

Parameter	Response
Histopathology Lung	Dose-related increase in alveolar macrophages minimal to slight at 500 mg/m^3 slight to moderate at 1500 mg/m^3 Pneumonitis in 4 of 6 males exposed for 3.5 hr to 1500 mg/m^3
Pulmonary function	Increased EEV
Lung weight	Wet and dry weights increased at 1500 mg/m^3
BAL protein	Increased at 1500 mg/m^3
BAL cells	Increased PMNs and total cells at 1500 mg/m^3
Hematology	No significant effects
AHH activity (liver)	Increased at 500 and 1500 mg/m^3
Zoxazolamine-induced paralysis time	Decreased at 500 and 1500 mg/m^3
Pentobarbital-induced sleeping time	No significant effects
Clinical Chemistry	No significant effects

Data taken from Grose et al.[36]

Of the pulmonary function parameters examined [End Expiratory Volume (EEV), Total Lung Capacity, Single Breath Diffusing Capacity to Carbon Monoxide, and Residual Volume], only EEV was affected. The EEV was elevated 21 percent in high dose animals but no significant changes in pulmonary function were found in low dose animals. According to the authors, the increase in EEV may reflect shallower breathing in response to exposure to a respiratory irritant.

In a 13-week subchronic study, rats were exposed to 500 and 1500 mg/m^3 for 4 hours/day, 4 days/week (Table 5). A concentration-related accumulation of macrophages was seen in alveoli and peribronchial lymph nodes. These lesions

TABLE 5

EFFECTS OF 13-WEEK EXPOSURE OF RATS TO HIGH DOSES OF FOG OIL MISTS

Parameter	13-Week exposure	4-Week recovery period
Histopathology Lung	Dose-related increase in alveolar macrophages minimal to slight - 500 mg/m^3 moderate to severe - 1500 mg/m^3 Focal hemorrhage - 1500 mg/m^3 Hyperplasia of peribronchial lymph nodes - 500 & 1500 mg/m^3	Granulomatous pneumonia at 1500 mg/m^3 (males)
Lung weight	Incr. at 500 and 1500 mg/m^3	Incr. at 1500 mg/m^3
Pulmonary function	No significant effects	No significant effects
BAL Protein	No significant effects	No significant effects
AHH activity (liver)	Incr. at 500 and 1500 mg/m^3	Incr. at 1500 mg/m^3
Zoxazolamine-induced paralysis time	Decr. at 500 and 1500 mg/m^3	No significant effects
Cytochrome P450 (liver)	No significant effects	No significant effects
Immunology	No significant effects	No significant effects

Data taken from Grose et al.[36]

were still present at the end of a 4-week, treatment-free recovery period. The significant increase in total cells in BAL fluid following exposure to 1500 mg/m^3 appeared to be due to an influx of PMNs. Congestion, focal hemorrhage and multifocal granulomatous pneumonia were observed in male rats treated with 1500 mg/m^3. Some granulomas were present at 13 weeks but most were not observed until after a 4-week recovery period which suggested development of a progressive lesion after cessation of exposure.

The final study conducted by Grose et al[36] examined the effects of 13-week exposures to fog oil at concentrations of 200 and 500 mg/m^3 (3.5 hours/day, 4 days/week) (Table 6). While there was no significant change in lung weight at 200 mg/m^3, there was a minimal to slight diffuse accumulation

TABLE 6

EFFECTS OF 13-WEEK EXPOSURE OF RATS TO LOW DOSES OF FOG OIL MISTS

Parameter	Response	
	200 mg/m^3	500 mg/m^3
Histopathology		
Lung	Minimal to slight incr. alveolar macrophages	Slight to moderate incr. alveolar macrophages
Systemic	Not significant	Not significant
Dry and wet lung weight	Not significant	Elevated
Pulmonary function	Not significant	Not significant
BAL protein	Elevated[a]	Elevated[a]
BAL cells	Not significant	% PMNs Incr.
Hematology	Not significant	Not significant
AHH activity (liver)	Elevated	Elevated
Zoxazolamine-induced paralysis time	Decreased	Decreased
Cytochrome P450 (liver)	Not significant	Not significant

[a]Occurred only in one of two replicate tests.
Data taken from Grose et al [36]

of macrophages in pulmonary alveoli. In addition, BAL protein and liver aryl hydrocarbon hydroxylase (AHH) activity were increased while there was a decrease in zoxazolamine-induced paralysis time. As the investigators suggested, the AHH elevation was probably induced by the PAH in the fog oil.

In this series of fog oil studies, the observed effects were restricted to the respiratory tract and liver enzymes. No changes in clinical chemistry, immune function or hematology were noted. The highest dose tested caused pneumonitis and progressive granulomas while signs of pulmonary inflammation were seen at all dose levels. The latter effects were progressively weaker as the concentration and frequency of dosing decreased. A no-observed effect level (NOEL) was not identified, as some changes were seen after a 13-week exposure to 200 mg/m^3, the lowest dose tested. In summary, 4- and 13-week inhalation exposures to fog oil mist caused inflammatory edema in the lungs of male and female adult rats while pulmonary function and gas exchange were not significantly compromised. Formation of granulomas at 500 and 1500 mg/m^3 after the 4-week recovery period suggested a progressive lesion in the lung following subchronic exposure.

Mouse Skin Painting Studies

Mouse skin painting studies have been used routinely for many years to evaluate the tumorigenicity of petroleum oil fractions (reviewed in references 11, 51 and 52). These studies typically involve repeated application of measured quantities of test oils or oil fractions to shaven skin on the backs of mice. The test material is applied 2 to 3 times weekly for a predetermined number of weeks or until the first appearance of papillomas. Time to tumor development (latent period), number of mice with tumors, and number of tumors per mouse are factored into the assessment of the carcinogenic potential of test samples.

Mouse skin painting studies have demonstrated that conventionally-refined mineral oils are carcinogenic[9,10,57,81,97] and that extensive refinement by severe hydrotreatment or solvent extraction reduces, or eliminates, the tumorigenic activity of mineral oils.[9,10,59] While naphthenic oils are usually more carcinogenic than paraffinic oils, mouse skin painting studies have shown that this is not always the case.[57]

It is widely accepted that the PAH content of the oils is responsible for their tumorigenicity. Bingham et al.[9,10] found a positive correlation between the tumorigenicity and the concentration of PAHs among one paraffinic and six naphthenic conventionally-refined oils. Jepsen[57] compared the tumorigenicity of a naphthene-based insoluble cutting oil, a solvent-extracted paraffin-based insoluble cutting oil, and an emulsifiable naphthene-based cutting oil before and after use. The tumor incidence was higher for used than for unused oils. *In vitro* studies by Payne,[76] Hermann,[42,43] and Schreiner and Mackerer[88] demonstrated that used oils are more mutagenic than unused oils. These changes in biological activity most likely result from the PAH and related compounds that are generated by pyrolysis as the oil is heated during use.[62,99,100]

The tumorigenic potency of lubricating and cutting oils is not always directly proportional to their PAH content. Stemmer and King[97] found that certain low boiling petroleum fractions and saturated subfractions with a low PAH content were carcinogenic to mouse skin. Haas et al. reported that oils with as little as 300 ppm PAH can be carcinogenic.[38] The carcinogenicity of oils with low PAH contents may be due to the presence of substances that enhance carcinogenicity (tumor promotors or co-carcinogens) or to the absence of tumor antagonists. It is now well established that conventionally-refined mineral oils contain co-carcinogens, tumor promoters and antagonists.[11,81,86] The concentrations of these agents vary widely among mineral oils which may account for the lack of a direct correlation between PAH content and tumorigenicity observed by some investigators.

Mehrotra et al.,[68] using a two-stage mouse skin bioassay protocol, demonstrated that jute batching oil can act as a tumor promoter. Initiation with single subcutaneous doses of urethane or 3-methylcholanthrene followed by skin painting thrice weekly for 15 weeks with a non-carcinogenic batch of jute oil induced benign papillomas, keratoacanthomas and fibrosarcomas.

Agarwal et al.[1] separated jute oil into three fractions (a PAH-free fraction, a fraction containing two- and three-ringed PAHs, and a fraction containing more than three-ringed PAH's) and tested them with a two stage mouse skin bioassay using 12-O-tetradecanoyl phorbol-13-acetate as a tumor promoter. Only that fraction containing three-ringed PAHs was active as a tumor initiator while only the original and reconstituted samples of jute oil could act as complete carcinogens on mouse skin.

The importance of solvent refining in reducing the content of potentially carcinogenic PAHs in lubricating oils was demonstrated by Bingham et al.[9,10] They examined the carcinogenicity of straight run petroleum distillates used as the base for cutting oils. The seven naphthenic and paraffinic oils tested had been conventionally-refined by extraction with 93 percent sulfuric acid and percolation through clay and were all tumorigenic on mouse skin. However, solvent-refined paraffinic or naphthenic oils did not induce tumors. No tumors were seen when elemental sulfur or organic sulfur compounds, which are widely used as additives in cutting oils, were added to the solvent-extracted oils. However, sulfur additives enhanced the number of tumors and time to tumor development in carcinogenic oils showing that these additives may act as tumor promotors or co-carcinogens.

In 1988, Gerhart et al. reported that solvent extracted lubricant base oil is neither a tumor initiator nor promoter on CD-1 mouse skin and is noncarcinogenic to C3H mice.[33] This work shows that solvent refining can remove tumor promotors and co-carcinogens as well as carcinogens.

Halder[39] showed that the severity of the refining process greatly influences the carcinogenicity of lubricating oils. Severe hydrotreatment and solvent refining can markedly reduce tumorigenicity; as expected, mild treatment by either of these processes is far less effective. Carcinogenicity was eliminated by following moderate solvent refining with mild hydrotreatment. In addition, blending of mildly hydrotreated oils with solvent refined oils led to substantial reduction or even elimination of

carcinogenic activity. Solvent refining with phenol, furfural or N-methylpyrrolidone were all equally effective in removing carcinogens. Unprocessed lower-viscosity lubricating oil distillates were substantially more carcinogenic than higher-viscosity distillates.

The work of Haas et al.[38] demonstrated that some of these findings are generalities that cannot be routinely applied to every situation. They showed that some severely hydrotreated or solvent refined naphthenic distillates were positive in mouse skin painting studies. In addition, unlike the work of Halder,[39] they showed that blending of some oils could increase, rather than decrease carcinogenicity. Thus, when two independently noncarcinogenic high and low viscosity oils were blended to produce an oil of intermediate viscosity, the final blend induced tumors on mouse skin.

Effects on the Reproductive System

Hoffman et al.[48] observed marked embryolethal and teratogenic effects following the application of used crankcase oil to quail and mallard duck egg shells. Unused crankcase oil was less embryolethal than used oil and caused no teratogenic effects. No evidence for reproductive or teratogenic effects in mammals was found in the literature.

IN VITRO TESTS

Salmonella/Ames Assay

While the standard Salmonella Ames/microsomal assay is a poor predictor of dermal carcinogenic activity of petroleum mixtures, modifications introduced by Hermann[42] and Blackburn et al.[12,13] have improved the sensitivity and reproducibility of the Ames assay for petroleum products. The modifications introduced by Blackburn include: testing a DMSO extract of the mineral oil dissolved in cyclohexane, the use of hamster liver S-9 metabolizing enzymes, and an increase in the concentration of nicotinamide adenine dinucleotide phosphate in the culture medium. In 1986, Blackburn developed a carcinogenicity index based on parameters of tumorigenic activity (e.g., latent period, number of animals with tumors) in lifetime skin-painting assays. The mutagenicity of 18 oil samples was ranked by this method and the correlation with potency rankings of the same samples determined from dermal carcinogenicity assays was excellent ($r = 0.92$). Blackburn concluded that the modified assay was sufficiently sensitive and reproducible to permit routine screening of individual refinery streams and blends which contain components with boiling points greater than 500°F.

Using Blackburn's modified Ames test and a mutagenic potency index based on linear regression analysis, Skisak et al.[92] ranked the mutagenic activity of 26 distillation fractions. Twenty of the oils tested were naphthenic lubricating oil base stocks without additives. A high level of correlation was found between determinants of tumorigenic potency in mouse skin painting bioassays and mutagenic activity in the Salmonella/Ames test.

Further studies by Venier et al.[102] showed that the mutagenicity of hydrotreated lubricating oils and other petroleum fractions is dependent on the boiling range of the base stock and the hydrogenation conditions, especially temperature and pressure. As expected, severe hydrogenation markedly decreased the mutagenic activity of lubricating oil base stocks, particularly of the light base stock. Hydrotreatment of a light naphthenic distillate with hydrogen pressures between 2000 and 3000 pounds per square inch at temperatures between 600 and 650°F yielded a virtually mutagen-free product. Mild hydrogenation was not nearly as effective. They found that "mild" hydrotreatment did not decrease the mutagenicity of a heavy naphthenic base stock and could actually generate mutagens in light naphthenic oils if excessive temperatures were used. Under all conditions tested, light naphthenics were less mutagenic than heavy naphthenic oils.

Other studies using the Salmonella/Ames tests have shown that mutagenicity is reduced by solvent refining.[42,43] "New" fog oil tested negative for mutagenicity with and without metabolic activation in four standard tester strains (TA97, TA98, TA100, and TA102) in the Salmonella/Ames assay.[63]

Other In Vitro Assays

The American Petroleum Institute reported that a solvent-refined, naphthenic-based lubricating oil stock, similar in viscosity (80 SUS at 100°F) to fog oil, was negative in the L5178 Y mouse lymphoma assay and did not cause chromosomal aberrations in the rat bone marrow cytogenetics assay.[17] Ingram and Grasso examined the effect of ten mineral oils on nuclear morphology in mouse skin cells.[50] For this test, oils were applied to the skin of female mice daily for 3 days. On the fourth day, mice were killed and the exposed skin removed and examined histologically. The investigators reported a good correlation between the induction of nuclear enlargement and carcinogenicity of mineral oils, as determined in mouse skin painting studies. A technical grade white mineral oil induced epidermal hyperplasia but no significant nuclear enlargement. An acidified oil and a hydrotreated oil caused a statistically significant increase in the incidence of enlarged nuclei. Both oils were known to be carcinogenic in mouse skin painting assays. Six of the remaining seven mineral oils were known to be noncarcinogenic while the seventh was an equivocal carcinogen. None of these oils caused nuclear enlargement.

Watson[108,109] subjected mineral oils to an <u>in vitro</u> mouse embryo fibroblast transformation assay modified to discriminate between initiating and promoting activities. The results showed that mineral oils may act as tumor promoters.

Human In Vitro Screening Tests

Sram et al.[95] conducted cytogenetic analyses of peripheral blood lymphocytes from 31 pressed glass makers who operated press-and-blow machines which released mineral oil mists containing relatively high concentrations of PAH. Worker exposures were less than 5 mg/m^3. The frequency of aberrant cells and the ratio of chromosome breaks per cell in mineral oil-exposed

workers were significantly greater than in matched controls. The investigators concluded that mineral oil aerosols generated by an automatic line of glass blowing machines are clastogenic.

CURRENT STANDARDS

The Occupational Safety and Health Administration (OSHA) and American Conference of Governmental Industrial Hygienists (ACGIH) have established 8-hour time-weighted average (TWA) exposure limits for mineral oils of 5 mg/m^3; the ACGIH also recommends a short-term exposure limit (STEL) of 10 mg/m^3 for mineral oil mists.[4] The STEL was apparently based on safety factors (slippery surfaces) rather than health effects.[104] The current OSHA and ACGIH limits are based primarily on the studies by Hendricks and Wagner[3,40,71,103] cited above.

CONCLUSION

Supplies of "old" fog oil may be stockpiled in war reserves and may find occasional use in training programs at military installations in the United States and abroad. Because contract numbers and order dates are not generally included in inventory lists, and the material in war reserves is classified, the quantities of "old" fog oil remaining at these locations cannot be readily estimated. Visual inspection of labels on warehoused drums would be necessary to distinguish between "old" and "new" fog oils.

The evidence that conventionally-refined mineral oils which are chemically similar to "old" fog oil can cause serious skin lesions and cancer of the skin of the arms, hands and scrotum is unequivocal.[52] The potential carcinogenicity of "old" fog oil would have to be considered in the development of an exposure standard. Permissible exposure concentrations based on such calculations would probably be so low that continuous masking would be required of everyone in the vicinity of fog oil mists. In this regard, the ACGIH is currently revising the mineral oil limit and may reduce the TLV for mineral oils containing PAHs to 0.2 mg/m^3 (as benzene-solubles) based on the ACGIH standard for coal tar pitch volatiles.[3,80] Reports of the PAH content of "old" fog oils vary between 14[110] and 50 percent.[60] With an exposure limit of 0.2 mg/m^3 for benzene-solubles, the total allowable exposure to "old" fog oil mists would vary from 0.4 to 1.5 mg/m^3. Breathing zone measurements taken by Young et al.[112] during unit training at Fort McClellan show that mineral oil exposures of soldiers working with fog oil smokes generally exceed 1.5 mg/m^3.

Since the current supplies of "old" fog oil are dwindling, in lieu of developing a military unique standard for "old" fog oil, it may well be advisable to prohibit its use as an obscurant smoke. If this is not possible, then continuous masking should be mandatory for all personnel in the vicinity of "old" fog oil mists. In addition to masking, skin exposures must be reduced to a minimum. Such exposures are difficult to control since the oils can readily penetrate standard military clothing and "suiting up" with proper protective apparel would be impractical for many of the situations under which fog oils are used. The current policy on smoke safety[72] states that "Showering and laundering of clothing following exercises will eliminate the

risk of skin irritation following exposure to smoke. Troops exposed to smoke should reduce skin exposure by rolling down sleeves." This statement should be modified to require washing of contaminated skin and clothing immediately after exposure to "old" fog oil. Because of the effort that must be taken to avoid overexposure to "old" fog oil, it is strongly recommended that stockpiles of conventionally-refined oils purchased before the promulgation of MIL-F-12070C, Amendment 2, no longer be used for production of smokes to which military personnel are exposed.

Skin Contact: "New" Fog Oil

Mineral oils can be rendered nontoxic to the skin by severe hydrotreatment or severe solvent refining. Specifications for severe solvent refining do not exist but it is commonly assumed in the petroleum industry that oils will be rendered noncarcinogenic when refined with a solvent to oil ratio greater than unity.[23] In contrast, oil manufacturers can treat lubricating oils as noncarcinogenic if they were hydrotreated according to process parameters specified by OSHA.[70] There is apparently no agreement within the petroleum industry that the OSHA specifications ensure a carcinogen-free product. Discussions with representatives from the petroleum industry indicate that while larger producers may use tests such as the modified Ames assay[12] or the FDA test for white oil purity,[30] many small producers rely on the process parameters specified by OSHA and do not subject their lubricating oils to further testing. The finding that oils refined in accordance with these criteria are not always noncarcinogenic,[38] leaves open the possibility that some lots of "new" fog oil may not be carcinogen-free if producers are using the OSHA specifications as a guideline. Because of this possibility, it is recommended that MIL-F-12070C be amended to include a requirement for tests demonstrating the absence of carcinogens. At a minimum, mutagenicity data as determined by the modified Ames assay of Blackburn[12] or PAH content, as determined by the FDA analytical test for white oil purity,[30] should be provided. In addition, detailed documentation of the means by which oil producers ascertain that fog oils supplied to the military are not carcinogenic should be provided to the Army by the supplier with each batch of fog oil.

It is further recommended that the current inventory of fog oil purchased after the fog oil specifications were revised in April, 1986 be examined to ensure that all batches are carcinogen-free. For this purpose, the FDA test for white oil purity as described by Haas should suffice. Because the viscosity of fog oil should be relatively constant in conformance with Military Specifications, unlike the regimen recommended by Haas, the only parameter which need be examined is UV absorbance. Since this test takes less than two days to complete, all batches can be tested expediently. Indeed, Wimer and Wright applied this test to samples of "old" and "new" fog oil and concluded that "The FDA test to predict dermal carcinogenicity is a relatively simple procedure to perform and should be useful in future work, not only on fog oil-related materials, but in other fields where petroleum fractions of various types are handled."[111]

Respiratory Efects

There are numerous case reports of humans with pulmonary lesions, such as granulomas and pneumonias, following oral or repeated nasal administration of food or medicinal grade mineral oils.[31,53,93] Scattered case reports suggest that occupational exposures to mineral oils may also cause pulmonary lesions.[22,78] Studies of the effects of inhaled mineral oils on animals are summarized in Table 7. In brief, short exposures to high concentrations of mineral oils can be tolerated by animals but repeated exposures may have debilitating effects. For example, Shoshkes found only scattered alveolar macrophages after single 2-hour exposures of mice to high concentrations (4300 mg/m^3) of mineral oil mists. Moderately severe foreign body reactions and occasional patches of lipid pneumonia followed 4-week exposures to the same concentrations.[90]

Lushbaugh found that monkeys were particularly susceptible to the effects of lubricating oils. Exposures to 63 mg/m^3 caused minimal effects in rabbits, rats and mice after one year, but caused pneumonia and pneumonitis in monkeys after as little as 44 days.[65] Selgrade et al.[89] and Grose et al.[36] observed pneumonitis in rats at the termination of a 4-week exposure to 1500 mg/m^3 fog oil. Progressive pulmonary lesions were observed after 13-week exposures to 1500 mg/m^3 fog oil. Although lubricating oils may vary in their relative toxicity,[65] both conventionally-refined oils equivalent to "old" fog oil[36,65,90] and highly refined mineral oils comparable to "new" fog oil[90,103] can cause pneumonia and pneumonitis.

A no-adverse-effect-level (NOAEL) was cited in only one animal study. Wagner showed that 1- to 2-year exposures to 5 mg/m^3 caused only occasional alveolar macrophages in the five species examined.[103] Adverse effects were observed with the lowest doses used in all other animal studies. The next highest dose level to which animals were repeatedly exposed was 63 mg/m^3.[65] This level caused no significant adverse effects in rodents but caused severe pneumonitis in monkeys. To err on the safe side, the human response should be assumed to resemble that of the most sensitive animal species. Thus, these data indicate that the permissible exposure level must be considerably less than 63 mg/m^3 (the lowest-adverse-effect-level) to avoid lipoid pneumonia. Based on the NOAEL of 5 mg/m^3 and the report that humans experience discomfort at mineral oil concentrations greater than 5 mg/m^3,[40,103] it is recommended that an 8-hour TWA exposure limit of 5 mg/m^3 (for the respirable fraction) be adopted by the U.S. Army. Some flexibility is inherent in this exposure concentration since most smoke blowing exercises are limited to 4-hour periods. Exposures encountered during this time would be normalized to an 8-hour day which would effectively increase allowable exposures to twice the exposure limit. To prevent excessive exposure, excursion levels as defined by the ACGIH[4] must be observed.

Measurements taken by Young et al.[112] during "operate and maintain" exercises at the U.S. Army Chemical School indicate that more than 50 percent of the cadre and students alike receive exposures greater than 5 mg/m^3 when 1 hour exposures are averaged over an 8-hour period. Young pointed out that these exposures can be reduced by altering work habits and conditions (e.g., leaving the immediate vicinity of the smoke generators except when absolutely

necessary). He noted that smoke generators used in these individual training exercises were deployed closer together than would be expected in combat and most unit training circumstances and postulated that reducing the number and proximity of generators would substantially reduce exposures. The introduction of such changes may suffice to reduce most exposures below the 8-hour TWA exposure level of 5 mg/m^3. However, masking is essential in those instances where work is performed in the immediate vicinity of the smoke generators. Half-face masks are recommended for such occasions.

Research Needs

The exposure standard of 5 mg/m^3 is essentially based on one rodent study.[103] The next highest dose evaluated in any study (63 mg/m^3) was severely toxic to monkeys.[65] Thus, the toxicity of the concentration range where many military and industrial exposures occur cannot be evaluated. Repeated-dose studies should be conducted to obtain data on the effects of exposure to fog oil mist concentrations between 5 and 63 mg/m^3. Because monkeys are apparently far more sensitive than rodents to lubricating oils,[65] these studies should be conducted in monkeys as well as rats and mice.

Although it is well established that refined oils can cause lipoid pneumonia, it is not known whether the development of this disease process can be exacerbated by the presence of additives or contaminants in the oils. This information is invaluable to standards setting since some of the data referred to in the current exercise were derived with conventionally-refined motor oils.[65] In addition, in times of war, motor oils may be substituted for fog oil if the latter is not readily available. Studies should be performed to determine the consequences, if any, of the use of such materials.

RECOMMENDATIONS

1. Stockpiles of conventionally-refined oils purchased before the Military Specification was amended to exclude carcinogens should no longer be used for production of smokes to which military personnel are exposed.

2. The Military Specification for fog oils should be further amended to include a requirement for tests demonstrating the absence of carcinogens. At a minimum, mutagenicity data, as determined by the modified Ames assay of Blackburn[12] or PAH content, as determined by the FDA analytical test for white oil purity,[30] should be provided by the manufacturer.

3. The current inventory of fog oil purchased after the specifications were revised in April, 1986 should be examined to ensure that all batches are carcinogen-free. For this purpose, the FDA test for white oil purity[30] should suffice.

4. An 8-hour TWA exposure limit of 5 mg/m^3 (for the respirable fraction) should be adopted for "new" fog oil. While some masking may be necessary with this exposure limit, in most situations the majority of soldiers will not be exposed to oil concentrations greater than 5 mg/m^3.

5. Repeated-dose toxicity studies should be conducted to obtain data on the effects of exposure to fog oil mist concentrations between 5 and 63 mg/m^3. The effects in mice or rats should be compared to those in monkeys.

6. Studies should be conducted to determine whether the development of pulmonary disorders can be exacerbated by the presence of additives or contaminants in mineral oils.

TABLE 7

ANIMAL STUDIES - INHALATION EXPOSURES

TEST MATERIAL	CLASS	SPECIES	CONCENTRATION (mg/m^3)	EXPOSURE DURATION	EFFECTS	REFERENCE
Light mineral oil 95% naphthenes 100% saturated	NFO	Dog, rat mouse, rabbit & hamster	5 100	12-24 mo	Occasional macrophage Granuloma (dog); Pneumonitis (rat) No effect (rabbit,mouse), Incr. AP levels (hamster).	103
NOAEL = 5 mg/m^3 LOAEL = 100 mg/m^3						
Fog Oil ("old")	OFO	Rat	500	4 wk	Macrophage accumulation (slight)	36
			1,500	4 wk	Pneumonitis	89
			200-500	13 wk	Macrophage accumulation (slight); incr. BAL protein & AHH activity.	
			1,500	13 wk	Granuloma, pneumonia; incr BAL cells.	
NOAEL = ND LOAEL = 200 mg/m^3						
Fog oil SGF, type No.1	OFO	Monkey, mouse rat & rabbit	63	12 mo	Both oils caused accumulation of macrophages but not inflammation in rabbit, rat & mouse. Monkeys much more severely affected; both oils caused pneumonia, pneumonitis, fibroplasia & gastritis in monkeys.	65
Auto lube oil SAE No.10	OFO	Monkey, mouse	132	12 mo		
NOAEL = ND LOAEL = 63 mg/m^3						
Liquid Petrolatum (USP)	NFO	Mouse	4,500	2 hr	Both oils caused scattered	90
SAE No. 10 motor oil	OFO		4,330	2 hr	macrophages, but no inflammation.	
Liquid Petrolatum (USP)		Mouse	4,500	4 wk	Both oils caused localized foreign	
SAE No. 10 motor oil			4,330	4 wk	body reactions of moderate severity.	
Medicinal grade mineral oil	NFO	Guinea pig	250	1 hr	No effect on pulmonary function	19
Laboratory grade paraffin oil	NFO		250	1 hr	No effect on pulmonary function	
SAE 10W-30 motor oil	OFO		250	1 hr	No effect on pulmonary function	
light lubricating oil	OFO		250	1 hr	Decrease in pulmonary compliance	

OFO = comparable to "old" fog oil; NFO = comparable to "new" fog oil

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